DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

JUL 6 2001

CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Ref: 01-HFD-45-0602

Robert E. Heinig, M.D.
Rochester General Hospital
300 Pearl Street, Suite 300
Buffalo, New York 14202

Dear Dr. Heinig:

Between July 17 and November 15, 2000, Mr. Andrew B. Paglia and Ms. Kim Downing, representing the Food and Drug Administration (FDA), met with you to: 1) investigate allegations of lack of patient care and potential data falsification; and 2) review your conduct of the following clinical studies:

1. Protocol [redacted] " The Effect of [redacted] on Morbidity and Mortality in Hypertensive Patients with Type II Diabetes and Diabetic Nephropathy" IND [redacted] and

2. Protocol [redacted] "Safety and Efficacy of Fixed Combination [redacted] Products as First Line Therapy in Patients with Type 2 Diabetes Melliitus Who Have Inadequate Glycemic Control With Diet and Exercise" performed for [redacted]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections, designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices. We note that at the conclusion of the inspection, Mr. Paglia and Ms. Downing presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We acknowledge your response dated December 7, 2000, and it will be included as part of your file. We concur that in the conduct of your investigations, you failed to meet your regulatory obligations as an investigator evidenced by your lack of direct involvement in conducting the studies as follows:

1. SUMMARY OF VIOLATIONS RELATED TO CONDUCTING THE INVESTIGATON ACCORDING TO THE SIGNED INVESIGATOR STATEMENT [21 CFR 312.53(c)(1)(vi)(c)]

You failed to provide staff members active in the conduct of the clinical trials direct supervision resulting in inadequate communication and lack of accountability between you and the research team which lead to dysfunctional interactions endangering the safety of subjects and termination of the study. Your failure to respond to staff inquiries regarding scheduled visits and laboratory evaluations may be attributed to the violations listed below

2. SUMMARY OF PROTOCOL VIOLATIONS [21 CFR 312.60]

You failed to conduct the study in accordance with Protocol [_____] in that:

a. The physical examinations were not performed in accordance with the protocol defined schedule for subjects 002, 003 and 005.

b. The study drug was not discontinued when subject 003's serum creatinine doubled since initial screening evaluation.

3. SUMMARY OF VIOLATIONS RELATED TO RECORDKEEPING AND CASE HISTORIES [21 CFR 312.62(b)]

You failed to maintain adequate and accurate records for Protocol [_____] in that no documentation in the subjects' records indicated that you reviewed and evaluated the laboratory reports for subjects 002, 003 and 005.

4. SUMMARY OF VIOLATIONS RELATED TO DRUG ACCOUNTABILITY [21 CFR 312.62(a)]

You failed to maintain drug accountability for Protocol [_____] in that:

a. Original drug logs were not maintained to account for amounts dispensed, ingested and/or amount of unused returned by subjects 002, 003 and 005. In addition, subject 005 received 102 tablets of level II that were assigned to subject 002.

b. Subjects 003 and 005 were not dispensed sufficient drug to cover time period between protocol required visits.

5. SUMMARY OF VIOLATIONS RELATED ASSURANCE OF IRB REIVEW [21 CFR 312.66]

You failed to obtain approval or inform IRB of changes in that:

a. You failed to obtain IRB approval for the media advertisement used to recruit and enroll subjects for Protocol[redacted]

b. You failed to inform the IRB in a timely manner that the informed consent used for the open label phase did not mention the Sustacal procedure. Subject 006 underwent the Sustacal challenge on 2/17/00 and the IRB was not notified until 10/24/00.

6. SUMMARY OF VIOLATIONS RELATED TO INFORMED CONSENT PROCESS [21 CFR 50.25 AND 50.27]

You failed to use adequate procedures in obtaining informed consent in Protocol[redacted] in that:

a. You did not obtain informed consent for the prescreening phase and prior to the initiation of the washout period when the subjects' routine therapy was discontinued for seven subjects.

b. The informed consent did not describe the wash out period or its duration as well as the risks associated with the discontinuation of ___

c. Outdated consent forms were used for subjects 004 and 008.

d. Informed consents signed at the time of the prescreening phase were discarded.

e. The informed consent for the open label phase did not indicate that a Sustacal load would be performed.

Because of the departures from FDA regulations discussed above and our receipt of the restrictions placed on your conduct of clinical research at Rochester General Hospital by your IRB, please inform this office, in writing, within 15 working days of your receipt of this letter, an explanation of the violations noted, a list of current studies you are involved in, and confirmation of whether you plan to conduct clinical research in the future. In addition, should you decide to conduct research in the future and request the restrictions placed on you by your IRB to be rescinded, what assurances will you provide to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in further regulatory action.

If you have any questions, please contact Dr. Antoine El-Hage, at (301) 594-1032, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practices II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

Martin H. Cohen, M.D.

Martin H. Cohen, M.D.
Acting Director
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